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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,400	10/10/2006	Ramon Merce Vidal	284330US0PCT	3489

22850 7590 05/04/2009

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EXAMINER	
COPPINS, JANET L	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
05/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/566,400	MERCE VIDAL ET AL.	
	Examiner	Art Unit	
	JANET L. COPPINS	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-38,41-47,49-66 and 69-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,21,35-42,44,45 and 49-66 and 69-74* is/are rejected.

7)☒ Claim(s) *2-19, 22-34, 43, 46, 47, 75 and 76* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19, 21-38, 41-47, 49-66 and 69-76 are now pending in the instant application.

Response to Amendment

2. Applicant's Amendment and Response, received January 8, 2009, has been reviewed by the Examiner and entered of record in the file. Accordingly, claims 39, 40, 67 and 68 have been cancelled and claims 49-66 and 69-76 have been amended.

Claim Rejections - 35 USC § 112

3. Claim 1 previously rejected under 35 USC 112, second paragraph for reciting, "...a stereoisomer thereof, an enantiomer thereof, a diastereomer thereof, a racemate thereof, a pharmaceutically acceptable salt thereof, or mixtures thereof.." Applicants contend that those compounds that would be stereoisomers, enantiomers, etc of instant formula (Ia) would be known to those skilled in the art, and therefore are not indefinite. The Examiner maintains that Applicants have still failed to designate any chiral centers, and have neglected to label any such *cis/trans* orientations or any enantiomeric rotations, furthermore the Specification also fails to designate any geometric or optical isomers within formula Ia and does not indicate any chiral centers or orientations. Therefore the rejection of claim 1 is maintained.

4. Claims 21, 35-42 and 44-45 previously rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for treating certain diseases such as anxiety, depression, eating disorders, etc., does not reasonably provide enablement for all of the diseases recited, including "cognitive memory disorders," Alzheimer's, M.S., Huntington's, psychoses, dementia, disorders of the CNS, schizophrenia, etc. The specification fails to provide

sufficient support of the broad use of the compound of the claim 1 for regulating a 5-HT_6 receptor, or for the treatment of all claimed neurodegenerative disorders and cognitive and personality disorders of claims 35-42 and 44-46.

Applicants have amended claims 21 and 49 in order to recite specific diseases, and have cancelled claims 39 and 40. Claims 49-66 and 69-74, previously drafted in terms of improper product-use claims, have been rewritten as method of use claims. Applicants argue that the rejections should be reconsidered in light of the fourteen references submitted, which discuss the relationship between the 5-HT receptor and the recited diseases/disorders.

The Examiner disagrees, and maintains the enablement rejection of claims 21, 35-38, 44 and 45, as well as claims 49-66 and 69-74, now directed to methods of use.
In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described in the previous Office Action.

The specification, while being enabling for compounds according to formula (Ia) for treating certain claimed diseases that respond to the regulation of the serotonin (5-HT) receptor, such as depression, anxiety, eating disorders, etc. does not reasonably provide enablement for treating all of the cognitive memory disorders, diseases, psychoses, dementias, etc listed by the above claims.

Applicants are claiming a method of treating many unrelated diseases, including diseases that are not enabled, such as Alzheimer's disease, multiple sclerosis, dementia, schizophrenia, Parkinson's, Huntington's, etc.

Serotonin receptors of the 5-HT6 subtype are known to be implicated in

diseases/disorders such as depression, anxiety, eating disorders, etc. Applicants have provided fourteen references which discuss the role of 5-HT serotonin receptors in learning and memory disorders, however these references alone do not provide specific evidenciary support that Applicant's instant claimed compounds are sufficient for treating said disorders. For example, please refer to the first page of the Madeline King reference, in the Introduction, "Learning and memory is currently a major area of research because not only do these processes underpin normal human behavior but they are also essential abnormal behavioral components in disorders ranging from addictions, anxiety, depression, schizophrenia, and neurodegenerative disease. There are currently **no effective treatments** for these learning and memory impairments so there is considerable interest in developing novel therapeutic approaches to treat this aspect..." (emphasis added). The remaining references discuss the 5-HT receptors and that compounds (however, not the instantly claimed compounds), which agonize or antagonize 5-HT **may** be useful one day for treating certain of these disorders or impairments.

Applicant provides no working examples which support the claim to a treatment of any specific diseases. Rather, Applicants provide an *in vitro* binding assay of the 5-HT6 subtype. Those of skill in the art recognize that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking.

The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a

particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that many differences exist between cultured cells and their counterparts *in vivo*.

These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This result has often led to tissue culture being regarded in a rather skeptical light, particularly when applicable to such complex, unpredictable diseases as those instantly claimed. Evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in cell-cell interactions. In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

There is no question Applicant's indoles may play a role in future methods of treating the aforementioned diseases/disorders. What is disputed is the claim that the compounds of formula (Ia) could be taken by a PHOSITA at the time of filing and used as treatments for the

neurodegenerative diseases/ cognitive memory disorders recited in claims, without undue experimentation. At the time of filing or even at present, the most which can be said about the compounds of formula (Ia) is that certain of the compounds possess the ability to bind 5-HT *in vitro*, and that references have been provided which suggest that compounds that agonize or antagonize 5-HT in murine studies **may** be useful one day for treating certain of the recited diseases. Moving from a discovered mechanism of action to a method of treatment requires a fallacious, inductive leap of logic amounting to undue experimentation. There is simply no evidence to be found in the literature suggesting that Applicant's compounds, or their structural cousins, are capable of being used in the manner recited in claims 21, 35-38, 44, 45, 49-66 and 69-74 . In essence, there is no absolute predictability in pharmacology, even with compounds whose properties have been determined, despite the extraordinarily high skill possessed by the ordinary artisan.

Another deficiency necessary for a PHOSITA to use Applicant's compounds to treat the recited diseases/disorders is dosage. So far, there is very little, if any, information to be gleaned from the literature on the subject of dosage relating indole-derivatives to those cognitive memory disorders or neurodegenerative diseases/disorders sought to be treated in the instant Application. There does not seem to be enough knowledge in the art to connect the instant compounds' properties to the actual treatment of the diseases/disorders claimed. It does seem that certain indole derivatives capable of agonizing or antagonizing 5-HT may provide useful therapeutic tools in future for treating certain of the diseases claimed. Although, at the time of filing, and even at present, a PHOSITA would not be able to use the invention as claimed.

Claim Rejections - 35 USC § 101

5. Claims 49-74 previously rejected under 35 U.S.C. 101 and 35 USC 1112, because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process; i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. Applicants have cancelled claims 67 and 68, and amended claims 49-66 and 69-74 such that they are now directed to methods of use. Therefore the 35 USC 101 rejections are withdrawn.

Claim Objections

6. Claims 2-19, 22-34, 43, 46, 47, 75 and 76 are objected to under 37 CFR 1.75(c) as being dependent on rejected base claims.

Conclusion

7. In conclusion, claims 1-19, 21-38, 41-47, 49-66 and 69-76 are pending in the instant application. Claims 1, 21, 35-42, 44, 45, 49-66 and 69-74 are currently rejected, and claims 2-19, 22-34, 43, 46, 47, 75 and 76 are objected to.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. COPPINS whose telephone number is (571)272-0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /

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April 27, 2009

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